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Review

Choosing between 7-, 10- and 13-valent pneumococcal conjugate vaccines in childhood: A review of economic evaluations (2006–2014)

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ABSTRACT

Background: Seven-valent pneumococcal conjugate vaccines (PCV7) have been used in children for more than a decade. Given the observed increase in disease caused by pneumococcal serotypes not covered by PCV7, an increasing number of countries are switching from 7-valent to 10- and 13-valent PCVs ("PCV10" and "PCV13"). Economic evaluations are important tools to inform decisions and price negotiations to make such a switch.
Objective: This review aims to provide a critical assessment of economic evaluations involving PCV10 or PCV13, published since 2006.
Methods: We searched Scopus, ISI Web of Science (SCI and SSCI) and Pubmed to retrieve, select and review relevant studies, which were archived between 1st January 2006 and 31st January 2014. The review protocol involved standard extraction of assumptions, methods, results and sponsorships from the original studies.
Results: Sixty-three economic evaluations on PCVs published since January 2006 were identified. About half of these evaluated PCV10 and/or PCV13, the subject of this review. At current prices, both PCV13 and PCV10 were likely judged preferable to PCV7. However, the combined uncertainty related to price differences, burden of disease, vaccine effectiveness, herd and serotype replacement effects determine the preference base for either PCV10 or PCV13. The pivotal assumptions and results of these analyses also depended on which manufacturer sponsored the study.
Conclusion: A more thorough exploration of uncertainty should be made in future analyses on this subject, as we lack understanding to adequately model herd and serotype replacement effects to reliably predict the population impact of PCVs. The introduction of further improved PCVs in an environment of evolving antibiotic resistance and under the continuing influence of previous PCVs implies that the complexity and data requirements for relevant analyses will further increase. Decision makers using these analyses should not just rely on an analysis from a single manufacturer.

1. Introduction

Streptococcus pneumoniae is a bacterial pathogen, with over 90 known serotypes. It causes invasive pneumococcal disease (IPD) such as meningitis, bacteremia, sepsis and peritonitis as well as generally milder non-invasive diseases such as pneumonia and acute otitis media (AOM) [1,2]. Treatment of pneumococcal disease is increasingly difficult due to rising antibiotic resistance [3,4].

A first pneumococcal conjugate vaccine (PCV) was introduced in the US in 2000 and this 7-valent PCV (PCV7) contains capsular polysaccharide antigens of seven serotypes (4, 6B, 9V, 14, 18C, 19F

Abbreviations: PCVs, pneumococcal conjugate vaccines; PCV7, 7-valent pneumococcal conjugate vaccine; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

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and 23F). At the time of the introduction, these seven types were responsible for 80–90% of IPD among children less than 5 years in the US and Western Europe [5]. The introduction of PCV7 vaccination in the US infant vaccination schedule not only substantially reduced IPD cases in vaccine recipients but also in the unvaccinated population through herd effects due to the reduced circulation of *S. pneumoniae* in all age groups following widespread vaccination of children. However, the use of PCV7 also led to an increase of IPD due to serotypes that were not included in the vaccine ("non-vaccine serotypes"), which thus gave rise to a "replacement effect" observed among both the vaccinated and the unvaccinated [6]. This led to the emergence of non-PCV7 vaccine serotypes. The extent of both herd and serotype replacement effects is country-specific [7].

Since 2010, two improved pneumococcal conjugate vaccines (PCVs) received market authorization in many countries, including in the US and the EU. These vaccines cover the seven serotypes included in the PCV7 vaccine, and additional serotypes responsible for an increasing proportion of IPD. Specifically, PCV10 ("Synflorix™", GSK) contains additional antigens from serotypes 1, 5 and 7F. The manufacturer claims a high protective effect against diseases not only due to pneumococcal serotypes but also against disease (most notably AOM) due to non-typeable *Haemophilus influenzae* (NTHi). PCV13 ("Prevenar13™", Pfizer) contains antigens from serotypes 1, 3, 5, 6A, 7F and 19A in addition to the PCV7 serotypes.

The clinical advantage of each vaccine is difficult to establish for each setting in which their use is considered. PCV10 may provide a higher protection against AOM, while PCV13 offers a wider coverage of serotypes causing IPD [8,9]. In relation to the latter, serotype 19A is of particular interest in many countries. The manufacturer of PCV10 claims that through coverage of related serotype 19F (also included in PCV7 and PCV13), PCV10 induces cross-protection against 19A IPD. This claim seems to be confirmed by recent studies in Brazil, Finland and Quebec [10–12], Recent data from the US and Europe show that herd immunity against 19A IPD has been induced by PCV13 use [13], but this has not been shown through PCV10 use. The choice between these vaccines must be made in a context of uncertainty regarding future serotype replacement, and differential vaccine prices. Policy should be based on population effectiveness, budget-impact, equity and cost-effectiveness. This paper aims to review all published economic evaluations of pediatric PCV10 and/or PCV13 from 2006 to 2014, and therefore focuses primarily on the aspect of cost-effectiveness.

2. Methods

An initial review of economic evaluations on PCVs predating 2006 [14] was followed by more recent reviews. However, these reviews had a particular focus, such as AOM [15], herd effects [16], studies from one country [17], a small group of countries [18], European countries [19] or modeling assumptions [20].

All cost data were converted to 2013 US dollars, based on Consumer Price Indices and exchange rates [21,22].

2.1. Search strategy

A literature search was undertaken using the broad combined search string "pneumococc* AND conjugat* AND (vaccin* OR immun*) AND "economic OR cost-effectiveness OR cost-benefit OR cost-utility OR cost-effectiveness OR cost-benefit OR cost-utility" in abstract, title or keyword fields of three databases: Scopus, ISI Web of Science (SCI and SSCI) and Medline (Pubmed) to retrieve studies of potential interest from 1st January 2006 up to 31st January 2014 (Fig. 1).

2.2. Selection

All initially identified studies were considered based on title and abstract, and included for further review if they contained a full economic evaluation [23] and evaluated a PCV covering more than 7 serotypes for use in children (<12 years). Non-English articles were excluded. A flow chart showing the selection process is illustrated in Fig. 1.

2.3. Data extraction

The inclusion criteria were checked by two reviewers (DBCW, PB), and data were extracted by either DBCW or PB using a standardized template. In case of doubt, there was a consultation process to base the extraction upon consensus.

3. Results

3.1. General study characteristics

We identified 63 economic evaluations published since January 2006 [24–86]. Thirty-one studies (49%) evaluated only PCV7, and were therefore excluded [56–86]. Four non-English studies on PCV10 and PCV13 were also excluded [52–55].

General study characteristics for the remaining 28 publications are presented in Table 1. These studies were made for countries covering 5 continents (7 in North America [24–27,35,36,41]; 6 in South America [27,29,33,38,41,50]; 6 in the Asia-Pacific [31,32,41,43,47,48,51]; 3 in Africa [28,41,49]; and 12 in Europe [27,30,34,35,37,39–42,44–46]).

3.2. Main assumptions and results

Eighteen studies provided analysis of both PCV13 and PCV10 [25,28,30–32,35–41,45,46,48–51] Seven studies included only PCV13 [26,33,34,42–44,47] while two studies only focused on PCV10 [27,29]. One study compared PCV11 with PCV7.

It is important to use the correct comparator in economic evaluations. For the PCV choices faced, a direct comparison of all potential PCV candidates is therefore essential [14]. Limiting the analysis to one PCV candidate, or using "no vaccination" as a comparator, when the current situation or the next best alternative is different is fundamentally misleading. At the time these studies were made, in most countries it would be most relevant to health policy to make an incremental CEA of using PCV13 vs. PCV10 vs. PCV7 [87–99]. As Table 2 shows, many analyses did not use a relevant incremental approach, reporting the cost-effectiveness of one or two vaccines vs. "no vaccination", and not all feasible options incrementally vs. the next best alternative at the time of the study.

Of the 28 economic evaluations [24–51], 10 studies were cost–utility analyses (CUA) [24–26,31,32,36,37,44,45,48], 7 were CEA [28,29,33,38,41,43,49], and 11 studies provided both CEA and CUA findings [27,30,34,35,39,40,42,46,47,50,51]. Twelve studies were conducted from a healthcare system or payer's [25,31,32,34,36,39,42,44–46,50,51] and 11 from a societal [24,26–28,30,37,38,41,47–49] perspective, while 5 studies adopted both perspectives [29,33,35,40,43]. The adoption of multiple perspectives enables the comparison of economic impact with and without incorporating indirect cost due to loss of productivity.

In terms of time horizon, five studies projected outcomes over 1 year [25,27,39,45,46], four studies for 5 years [28,32,40,47], four studies for 10 years [26,42,43,51], four studies for 20 [33], 25 [29], 30 [44] and 100 years [31], respectively. Ten studies used lifetime as a time span [24,30,34–38,41,48,50]. Most studies applied discount rates between 3% and 6% to cost and benefits. In all five studies with 1-year projection, costs and outcomes were not discounted.